

## California Cancer Commission Studies\*

### Chapters XXIV and XXV

# Cancer of the Bladder

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**A**SH, after recording 3,200 cases of epithelial tumors of the bladder in the Tumor Registry of the American Urological Association, constructed the following average case from the statistics of the Registry: The patient is a white man aged 60. The chief complaints are hematuria and dysuria. Cystoscopic examination reveals a single papillary tumor located on the posterior surface of the base of the bladder. Pathologic study reveals papillary carcinoma, grade I or II. The prognosis is repeated recurrence in spite of treatment; the patient has about one chance in three of living five years and about one chance in 25 of complete recovery.

Most of the 3,200 patients represented by these case histories have been operated upon by men skilled in diagnostic and surgical urology, men capable of carrying out the type of treatment best suited for each individual case. Under these circumstances and with these figures before us, tumor of the bladder appears as an extremely lethal disease. In large part this depressing mortality is not due to the lack of response to treatment, or the incurability of bladder tumors, but to the excessively long period of time in which the tumors were allowed to progress unmolested. In a report of over 200 cases published in 1946, it was stated that an average of 12 months elapsed from the time the patient had the first symptoms "pointing the accusing finger at his bladder" until he presented himself to the urologist for diagnosis and treatment. In a published report of 135 cases of bladder tumor seen at the Los Angeles County General Hospital, 36 were so far advanced that no satisfactory treatment could be employed and in eight cases merely palliative cystotomy was undertaken. In all of these 44 cases, almost one-third of the total entry, the patients died in the hospital.

Another interesting commentary on the usual delay in the diagnosis and treatment of these tumors is that only 112 of 658 Registry patients (18.5 per cent) came under observation when the tumor was less than 2 cm. in diameter. This delay in receiving treatment in some cases is due to the lack of understanding of the portent of the symptoms on the part of the patient. One woman had blood in the urine almost continuously for ten years from the age of 40 to 50 years. She considered this to be an unusual type of menopause and did not seek treatment until sacral metastases caused severe pain.

In a fairly large number of cases delay is due to inaction, reassurance or symptomatic treatment

on the part of the physician. It is not uncommon, by any means, to see patients who received advice and medical treatment for hematuria and bladder symptoms for years before cystoscopy finally is done. In some cases a urologic examination is suggested by the physician but not insisted upon; *it should be the duty and obligation of the physician who first sees these patients to make certain that the cause of hematuria or other symptoms is immediately determined.* Early observation would also aid the examining urologist, as the best time to determine the source of the bleeding is during the first attack, while the patient is still bleeding. Delay permits the growth to increase in size and to spread to layers in the bladder wall from which metastasis readily occurs.

#### CLINICAL DATA

*Age and sex.* The age of the patient is important; young adults stand the shock of operation well, but they often have extensive growths of a high degree of malignancy. In infants and in persons more than 60 years of age, the operative mortality is very high. In the Bladder Tumor Registry, which represents the age incidence in this country, the peak is reached between the ages of 60 and 64 years. Of 921 epithelial tumors, 160 (17.4 per cent) occurred at this age period. Of the 921 registered, 61.8 per cent occurred between the ages of 50 and 69 years.

The sex incidence of bladder tumors has been well established and seldom varies in published reports. Of 902 epithelial tumors of the bladder in the Carcinoma Registry, 684 (74.3 per cent) were found in the male, 213 (23.7 per cent) in the female; in five cases the sex was not stated. It has been found that among patients under 50 years the tumor in both sexes was of high degree of malignancy in 50 per cent of the cases, whereas among the patients after the age of 50, carcinoma of low grade predominated. There seemed to be no relation between sex and grade of malignancy.

*Size of tumor.* The size of the tumor when first seen is related to the result at the end of five years. In one hundred and twelve of 658 Registry tumors which were less than 2 cm. in diameter when first seen, the largest percentage of five-year "cures" was obtained, namely, 34 cases (30.3 per cent). When the tumor varied from 2 to 5 cm. in diameter, 82 of 309 patients, or 26.5 per cent, survived five years. However, when the tumor was larger than 5 cm., in only 35 of 222 cases (15.8 per cent) was the growth under control for five years.

\*Organized by the Editorial Committee of the California Cancer Commission.



Figure 1.—Small pedunculated papilloma, base of the bladder.

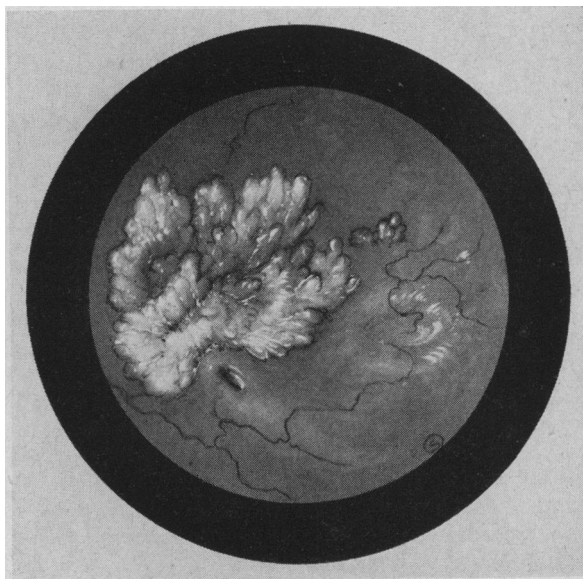


Figure 2.—Papillary carcinoma, grade II malignancy.

**Location of tumor.** About one-third of all tumors occur in the area of the trigone and about an equal number on the lateral walls. Ten per cent occur at the neck of the bladder and about as many on the posterior wall. A small number occur in the vault and on the anterior wall. In about 50 per cent of cases more than one area is involved.

#### PATHOLOGY

Practically all tumors of the bladder are epithelial in origin and may be divided into three groups; papillomas, papillary carcinomas and solid infiltrating carcinomas.

1. *Papillomas.* Simple papillomas consist of a short stalk projecting from the bladder mucosa, composed of a free, central blood supply covered with connective tissue and several layers of epithelium of adult bladder type. They vary from several mm. to 2 cm. in size (Fig. 1). *It is advisable to consider these growth not as benign lesions but as low grade epitheliomas.* Regardless of the gross or microscopic appearance many of these tumors are clinically malignant; they metastasize and recur frequently and even though early microscopic sections show no evidence of malignancy, the recurrences and metastatic deposits reveal definite malignant changes.

2. *Papillary carcinomas.* These tumors, called malignant papillomata by some pathologists, are limited in size only by the capacity of the bladder. They retain their pedicle and are composed of clubbed fronds with a marked irregularity of outline (Fig. 2). They are of a moderate degree of malignancy. In one group of 71 patients with papillary carcinoma of the bladder 26 (36.6 per cent) were dead after an average postoperative period of 11.5 months. Twenty (76.9 per cent) of those who died from malignant papillary carcinoma died in the first year after operation; 45 patients (63.3 per cent) were living an average of two years following operation.

3. *Solid carcinomas.* These tumors are of two types: the widespread papillary epithelioma, and the low, flat, infiltrating carcinoma (Fig. 3). The former has a rolled-out advancing border, the upper surface often being covered with short, stubby, papillomatous protrusions, or the top may have sloughed off, leaving a flat, ulcerated surface. These tumors, sometimes firm, are often soft, flabby and friable, and can easily be scraped off the surface of the bladder. The histological picture shows the relation of this tumor to the papilloma. In the infiltrating type the margins slope outward to meet the mucosa and burrow down into the wall of the bladder. These tumors are generally firm and compact, and without a tendency to split in cleavage planes. These solid carcinomas are the most malignant of the epithelial growths of the bladder. Sixty-seven (71.2 per cent) of a group of 94 patients with solid carcinoma were dead after an average postoperative period of 7.5 months. Fifty-nine (88 per cent) of these died the first year after operation. Twenty-seven living patients have lived an average of three years and three months.

There are a number of rarer tumors of the bladder, such as squamous cell carcinoma, adenocarcinoma, myxoma and sarcoma, which are of clinical as well as histologic interest. Benign ulcers may occur in association with infection (Figure 4).

*Squamous-cell carcinomas.* These tumors are distinct individual types of epithelial growths. Their onset is insidious, their growth is rapid, and they cause few distinctive symptoms. They probably develop from metaplastic bladder mucosa which has undergone epidermization as a result of irritation from infection or formation of stones. The tissue in most cases is firm and friable. The growths involve the wall of the bladder extensively, and are flat and frequently ulcerated; the lateral margins

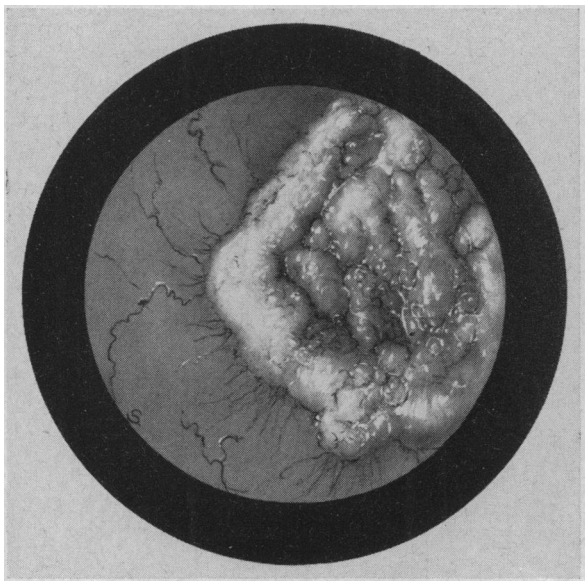


Figure 3.—Solid carcinoma in the left bladder base obstructing outlet of left ureter.

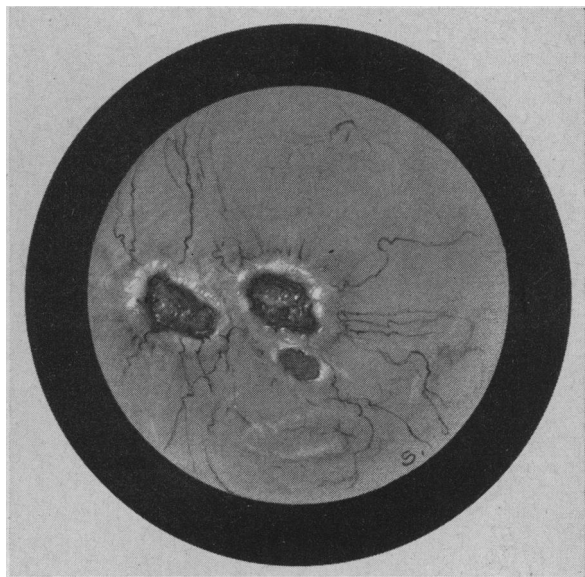


Figure 4.—Benign ulcer of bladder associated with urinary tract infection.

slope out toward the mucosa, sinking deep into the underlying tissues. Sometimes patches of leukoplakia, giving a clue to the origin of the malignancy, are found in the region of the tumor. Squamous-cell growths are most often found in early middle life and are not uncommonly preceded by evidence of long-standing cystitis. Compared with other epithelial tumors, these growths occur relatively more often in females. While metastasis is not uncommon, death in most instances is due to the obstruction and infection resulting from the local lesion. The histological examination generally shows marked cellular activity.

#### SYMPTOMS

*Hematuria.* Hematuria is the cardinal symptom of tumor of the bladder. It is the most important first signal to the patient or his doctor that a bladder tumor may be present. It is the red flag of danger that, disregarded on first appearance, may not show a second time until the growth has progressed to a dangerous stage.

The characteristic hematuria of tumor is spontaneous, profuse, painless and total. Tumors located near the vesical outlet may bleed slightly with onset of micturition or there may be terminal bleeding. Usually the period of bleeding is short and brisk and the interval between spells varies from days to months. This bleeding may be the sole symptom of tumor for a long time, and, as Keyes states, its very character encourages both patient and physician to pretend to themselves that the bleeding is unimportant. The tumor bleeds briefly. The patient takes a "sure" cure. The bleeding stops. It is agreed to wait to see what will happen next. A year goes by before any decision is reached—a year in which the tumor is growing, becoming larger, more difficult to control.

It is difficult to believe that of 508 cases from the carcinoma registry with initial hematuria, only half were diagnosed in the first year. Moreover, 20 per cent had to wait three years for a diagnosis and 26 cases actually were not diagnosed for seven years or more. In only one-third of these cases did the patient survive five years or more. In contrast to this surprisingly low survival in these late cases is a group of reported cases in which 142 patients with bladder tumors were cystoscoped and treated shortly after the first attack of hematuria; in all but three cases the growths were small early tumors which responded readily and favorably to treatment.

*Dysuria and frequency.* Painful or frequent urination is not a common accompaniment of bladder tumors, especially in the early stages of the disease. In the Registry group of cases, frequency, occurring in 15 per cent of cases at the onset of the disease, occurs in 70 per cent of cases later. This later increase is due to infection and obstruction and in some cases to extensive involvement of the bladder. In many cases there is surprisingly little bladder pain even in cases where only a small amount of bladder mucosa remains. This lack of pain is responsible for much of the procrastination in seeking treatment. Many people believe that nothing serious can occur without pain. It is not unusual to find patients who, having ignored intermittent attacks of frequency and hematuria for years, apply immediately for treatment when an extension of the growth causes pain.

#### DIAGNOSIS

Single or repeated attacks of spontaneous hematuria suggest the diagnosis of tumor, and the diagnosis is made by cystoscopy. Between bleedings the urine may be blood tinged or red blood cells may be found microscopically, although the absence

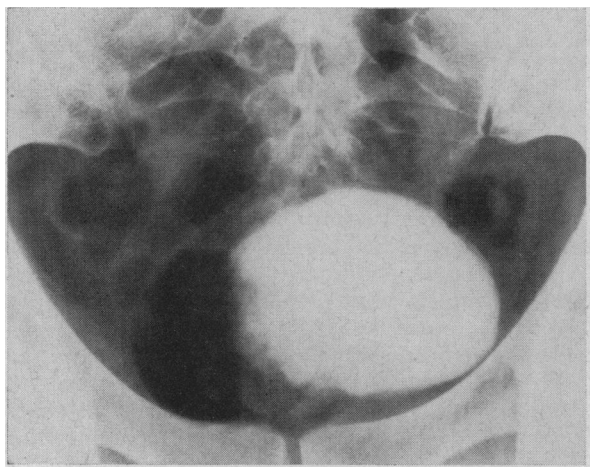


Figure 5.—Cystogram revealing comparatively small papillary tumor of right base.

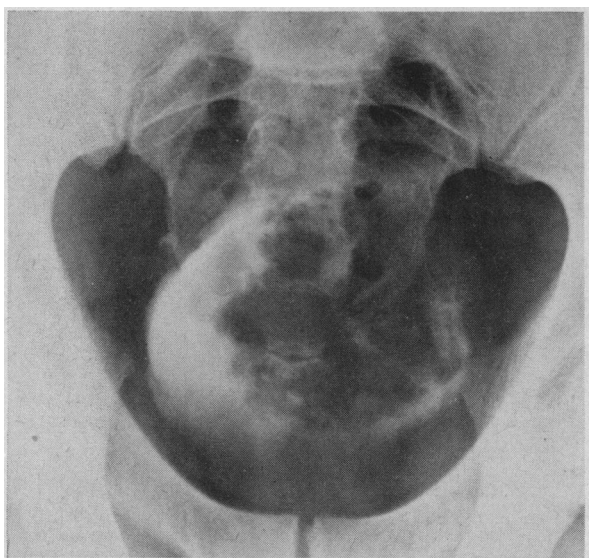


Figure 6.—Papillary carcinoma of large size. Tumor was pedunculated, of low degree of malignancy, and a good result was obtained following its removal.

of blood cells does not indicate that there is no tumor. *All patients with hematuria should be cystoscoped* by one skilled in this procedure. It is essential that the examination be painless for the examiner's sake as well as that of the patient. If there is pain with cystoscopy, not only does the patient suffer but it is also impossible for the cystoscopist to make a thorough examination. Intravenous pentothal or caudal anesthesia usually gives sufficient anesthesia for an accurate, unhurried examination. The number, size, and locations of the tumors should be noted, the base or pedicle observed and a specimen of the tumor removed for histologic examination. Cystograms are helpful in estimating the extent of vesical involvement as shown by filling defects. It may show a much more extensive involvement than would be noted by cystoscopic examination and it is also helpful in the presence of a massive pedunculated tumor when an accurate cystoscopic



Figure 7.—Solid carcinoma covering upper third of bladder surface.

estimate cannot be made of the actual involvement of the vesical wall (Figures 5, 6, 7, 8, 9).

It is not always possible or desirable to catheterize the ureters, but some knowledge of the upper urinary tract should be obtained. This data can be obtained with an intravenous urogram which is of great help in determining the patency of the ureters and also gives a fairly accurate indication of the function of each kidney.

Hematuria in men of an age at which prostatic obstruction occurs is very commonly thought to be prostatic in origin, and on this account examination is at times delayed. One patient, an intelligent physician, aged 56, had repeated attacks of hematuria over a period of two years. He had been told the bleeding was probably prostatic, so cystoscopy was delayed. When finally it was done, there were one large papillary tumor on the lateral wall, numerous small tumors in the base and the entire prostatic urethra was filled with small papillomata.

All bladder tumors should be considered as potentially malignant. The size, location, number of tumors and the degree of penetration of the growth can be determined at the first examination. At this time a biopsy specimen should be taken.

It is not always possible by cystoscopy to determine the size of the base of the tumor or the degree of penetration into the bladder wall, for, in some cases, a tumor which appears to cover a large area of the bladder wall may be found on surgical exploration to have a small, compact pedicle. Bimanual pelvic examination should always be done, as in this way an estimate can be made of the extent of tumor infiltration especially about the bladder neck, the trigone, and the fundus.

Satisfactory equipment should be available to coagulate or treat the tumor if it is of a size to be



Figure 8.—Solid carcinoma of right side of bladder.

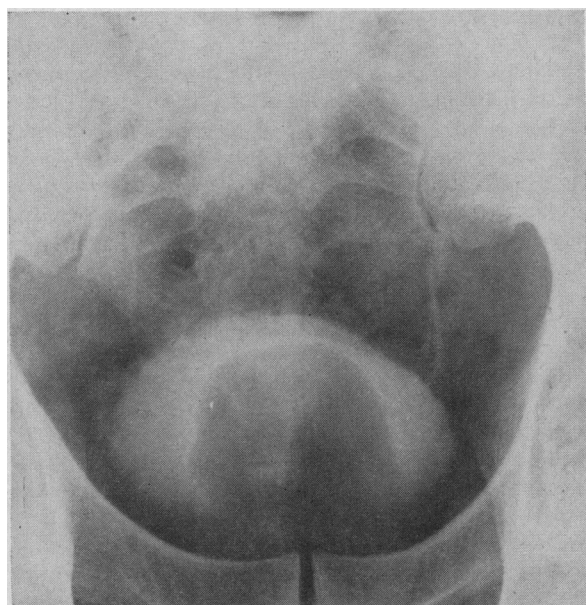


Figure 9.—Filling defect caused by hypertrophied prostate.

controlled by simple measures; if not, the required method of treatment should be decided on at this time. This is a procedure requiring considerable skill for proper performance.

#### TREATMENT

Collected groups of statistics indicate that treatment for tumors of moderate or large size is followed by a high mortality. Usually the patients requiring surgical operations are seen late in the course of the disease. The great majority of tumors requiring operation started as small papillomata of a low degree of malignancy which would have been readily amenable to treatment by simple transurethral procedures. The number of cases of papillomata, po-

tentially malignant, but successfully treated by a skillful urologist as a routine office procedure is far greater than the number requiring extensive surgical operations. Certainly many cases are treated in the early stages with excellent results. The important thing is to find more of these cases, or all of them, while they are amenable to the simpler methods of treatment; when this occurs extensive surgical procedures will rarely be necessary.

The method of treating bladder tumors has changed rapidly in the last two decades and at present it varies considerably in different clinics. Exponents of certain methods of treatment such as x-ray and radium therapy and cystectomy have reported improved results in the treatment of their cases and thus influenced the general trend of treatment for a period of time. There is no single procedure that is suitable for all cases. *The best results have been obtained by operators with experience and judgment who are able to select the best treatment or combination of procedures for each individual case.*

The following methods of treatment of bladder tumors are most commonly employed at the present time.

1. *Transurethral procedures.* Transurethral procedures such as fulguration implantation of radium emanation seeds and removal of the tumor with the resectoscope should be done only in those areas that are readily accessible through the cystoscope. Papillomas up to 2 cm. in size can usually be controlled by simple fulguration. Larger tumors are generally considered malignant; nevertheless many, if they are not too large, respond to fulguration. If the tumor does not respond to three or four fulgurations, some other method of treatment is desirable.

For tumors too large to respond to fulguration transurethral resection when used by operators skilled in the use of the resectoscope gives good results especially with tumors of a low grade of malignancy. The removal of a solid tumor from a thin walled bladder with proper coagulation of the base is a delicate and risky procedure that calls for a high degree of technical skill. Recently many cases have been reported treated by this method with good results and low mortality. The tumor is resected sufficiently deep to expose the muscular layer of the bladder wall and this area then coagulated. Tumors weighing as much as 100 gm. have been removed in this manner. Following resection of tumors with a large base or those which have infiltrated the bladder wall, radon seeds may be implanted in the coagulated area as a further aid toward preventing recurrence. It is only in exceptional cases that the use of the prostatic resectoscope by the average operator is indicated. Many urologists advise against its use, favoring open methods of treatment.

2. *Suprapubic treatment.* The type of open surgical treatment employed depends on the extent and location of the growth. About 40 per cent of tumors occur on the lateral walls and in the vault, areas suitable for the removal of a segment of the entire vesical wall through a suprapubic opening. The

best results are obtained with this method of treatment, often called segmental resection, and it should be carried out whenever possible. The tumor and the entire thickness of the bladder wall should be resected with a cutting current which aids in the control of hemorrhage and avoids the spread of tumor cells in the operative field. A margin of normal bladder wall 1 cm. or more in width around the periphery of the tumor should be included in the resection. If the growth is comparatively small, or of a low degree of malignancy, or if it is an area unsuitable for resection, it may be excised with a portion of the bladder wall. The base is then thoroughly coagulated with a diathermy electrode and radon seeds planted if further treatment seems necessary.

Electrocoagulation or diathermy is the method of choice in destroying the flat, fairly extensive papillary growth of a low degree of malignancy. Occasionally growths which are apparently so extensive as to be inoperable respond surprisingly to thorough coagulation. On this account coagulation should be carried out, if possible, in patients with tumors that are seemingly inoperable; in a number there will be regression of the tumor.

There is a small group of cases in which the tumor is still confined to the bladder but is so located or so extensive as to preclude any possibility of cure by the usual methods of treatment. Cystectomy has been done in a number of these cases and reports of results have been increasingly more favorable. The mortality is high and the survival rate low, although in a group of recently reported cases satisfactory results have been obtained. Cystectomy demands that the urinary stream be diverted, which is usually carried out as a preliminary procedure. The bladder is then resected at a second operation. In some cases both procedures have been carried out at the same operation.

3. *Irradiation therapy.* High voltage x-ray therapy should be reserved for use in inoperable cases, for palliation and the arrest of hemorrhage. It is best suited to cases with a high degree of malignancy, as radiosensitivity tends to increase in proportion to malignancy. In occasional isolated instances x-ray therapy produces startling regression of the tumor. In those cases where, for various reasons, other more dependable methods cannot be employed, it may be of benefit.

There is little evidence to show that malignant tumors of the bladder can be cured by high voltage

irradiation. Most urologists believe that it should be used only for patients who have advanced tumors, or for old and debilitated patients. In any case in which operation is suitable, it should be done.

4. *Implantation of radon.* Radon seeds have a definite place in the treatment of tumors of a high grade of malignancy. These seeds may be used in association with irradiation but they are most frequently employed following electrocoagulation. In tumors where seeds have been planted preoperatively through the cystoscope the proliferative power of the tumor cells, as observed postoperatively, is markedly reduced and in some cases completely destroyed. In other areas, nests of apparently intact malignant cells may be found. What benefit might be obtained by preoperative treatment is nullified by the increased technical difficulty of later surgical removal. The edema, swelling and friability of the irradiated tissue make it difficult and at times almost impossible to resect and close the bladder wall. On this account preoperative radium treatment is now rarely used.

#### SUMMARY

Tumors of the bladder, when treated during the early period of symptoms, respond readily to treatment and results can be obtained which are comparable to those obtained following treatment of tumors occurring in other parts of the body.

*Intermittent hematuria is the most frequent and outstanding symptom of bladder tumor.* Its prompt and complete, temporary disappearance, together with the lack of pain and discomfort, gives the patient and often the physician a false sense of reassurance, inviting procrastination in examination and treatment. Unfortunately, bleeding may not recur until a regrettably long period of time has elapsed.

*Hematuria is always serious;* it should never be ignored without definitely determining its origin. This necessitates a cystoscopic examination. If this is done as a routine measure, it will be possible to reduce substantially the distressingly high mortality from tumor of the bladder.

Given an early case, the chance of cure for the patient with a bladder tumor is dependent in large part upon the skill, knowledge, and experience of the cystoscopist.

*"Cysts and Tumors of the Jaws," by Eugene W. Demaree, M.D., Chapter XIII of the California Cancer Commission Studies will appear in this section of the January number of CALIFORNIA MEDICINE.*

#### Correction

The name of one of the authors of Chapter XXII of the California Cancer Commission Studies, which appeared in the September issue of CALIFORNIA MEDICINE, was misspelled. The chapter, titled Carcinoma of the Liver, Gallbladder, Extrahepatic Ducts, and Pancreas, was written by William F. Roe, M.D., of Van Nuys, and E. Eric Larson, M.D., of Los Angeles. Dr. Roe's name was misspelled "Rowe."